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Carotid Intima-media Thickness, Carotid Wall Shear Stress and Restenosis After Femoro-popliteal Percutaneous Transluminal Angioplasty (PTA)

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Objective. *To determine the relationship between carotid intima-media thickness (IMT), carotid wall shear stress (WSS) and restenosis after femoro-popliteal percutaneous transluminal angioplasty (PTA).*
Patients and methods. *Thirty-one subjects (18 men, 13 women, median age 69 years) treated with femoro-popliteal PTA for symptomatic peripheral arterial occlusive disease were enrolled. On admission, IMT, internal diameter and blood velocity of the common carotid artery (CCA) were assessed by high-resolution ultrasonography. Blood viscosity was measured and carotid WSS was calculated. Patients were followed up for 6 months for the occurrence of significant restenosis (>50%) as documented by duplex ultrasonography. Two patients were lost to follow-up.*
Results. *Fourteen patients (48%) developed restenosis at 6 months. IMT and WSS were not different in patients without and with restenosis (IMT: 0.90 (0.85–0.97)* vs. *0.89 (0.84–0.93) mm*, $p=0.51$; *WSS: 14.1 (11.9–19.2)* vs. *15.9 (12.8–21.5) dyne/cm*^{2}, $p=0.48$).
The hazard ratio of incident restenosis as estimated by Cox regression analysis was 0.04 for IMT ($p=0.23$; *95% CI 0.0001–8.22) and 1.07 for WSS* ($p=0.10$; *95% CI 0.98–1.17).*
Conclusions. *In this pilot study involving a limited number of patients, carotid IMT and carotid WSS are not significantly related to restenosis at 6 months after femoro-popliteal PTA. This might be the result of different underlying pathophysiology for atherosclerosis and restenosis.*

Keywords: Carotid intima media thickness; Carotid wall shear stress; Balloon angioplasty; Restenosis; Femoropopliteal segment.

Introduction

After primary successful angioplasty of the femoropopliteal arteries restenosis occurs in approximately 30–40% of the patients within 6 months after the initial intervention.[1,2] The development of restenosis is complex and is caused by intimal proliferation. Intimal proliferation occurs after endothelial injury, leading to mobilisation and accumulation of platelets, release of growth factors, and proliferation and migration of smooth muscle cells.[3–5]

Carotid artery intima media thickness (IMT) is a well established indicator for early generalized atherosclerosis.[6–8] IMT has significant predictive value in assessing the risk for cardiovascular and cerebrovascular events.[9–12] Several studies have shown a strong correlation between increased IMT and peripheral artery occlusive disease (PAOD).[13–15] Furthermore, low wall shear stress (WSS) has been identified as a local risk factor, being involved in arterial remodelling and atherogenesis.[16] WSS in the common carotid artery (CCA) is decreased in patients with vascular risk factors[17,18] and in those with symptomatic peripheral arterial disease (unpublished data).

Currently, the relationship between carotid IMT and carotid WSS and the occurrence of restenosis after percutaneous interventions in peripheral arteries has not been investigated.

As restenosis after percutaneous transluminal angioplasty (PTA) and atherosclerosis share many pathophysiological features, the aim of the present study was to investigate the relationship between carotid IMT, WSS and restenosis after femoropopliteal PTA.

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Materials and Methods

Patients and procedure

This prospective study was performed on patients referred to the Division of Angiology, University Hospital Zurich, Switzerland, for symptomatic PAOD (Fontaine stages II to IV). The study protocol was approved by the local ethics committee, and all participants gave informed consent. Consecutive patients treated with femoro-popliteal PTA because of at least one significant lesion, proven by angiography or duplex ultrasonography, of the femoropopliteal artery were included. Over a period of 4 months, all patients admitted for PTA of the femoropopliteal segment were screened. Patients that did not fulfil one of the exclusion criteria or who were not simultaneously in another study were enrolled. Patients with non-atherosclerotic diseases, with bypass graft lesions, with concomitant stent implantation as well as patients in whom the procedure was primarily not successful (defined as inability to pass the lesion with the guidewire, or residual stenosis $\geq 50\%$ as demonstrated by duplex ultrasonography the day after the procedure) were excluded. Further, patients with a history of carotid thrombendarterectomy, carotid stenting or carotid stenosis $>50\%$ were excluded also.

Angioplasty was performed using standard catheters, guidewires and balloons. Balloon size, usually between 4 and 6 mm, was chosen by the operator according to vessel size. Balloon pressure and inflation time were at the operator's discretion.

Nineteen patients were treated for lesions in the superficial femoral artery (ten for a single lesion, nine for multiple, i.e. at least two, lesions). Seven patients had their angioplasty in the distal femoral (Hunter's canal)-proximal popliteal segment (two of whom had a single lesion, five multiple lesions). In five patients, PTA was performed in the popliteal artery (four single, one multiple lesion).

Exact anamnestic data were collected. The Fontaine classification was used to determine the severity of PAOD, i.e. stage II (claudication) or stage III (critical limb ischemia with persistently requiring regular analgesia for >2 weeks).

The patients underwent baseline clinical examination including palpation of peripheral pulses and ascultation of bruits. Non-invasive basic assessment of PAOD with pulse volume recordings and ankle-brachial pressure measurements by Doppler ultrasonography for calculation of the resting ankle-brachial index (ABI) also were performed.

All patients received 100 mg acetyl salicylic acid/day. PTA was performed using standard guidewires and balloon catheters. All patients received 5000 units heparin (i.a.) during the procedure and 5000 units of a low-molecular weight heparin (dalteparin)/day for 48 h after the intervention.

Carotid ultrasound

The carotid arteries were evaluated at baseline with high-resolution B-mode ultrasonography (Acuson XP 128) using a 7.5 MHz linear transducer probe. The IMT of the CCA was defined as the mean of 24 measurements taken of the near and far wall on both the left and right sides, each recorded from an anterolateral, mediolateral and posterolateral position. Zoomed images of the CCA on which the intima-media boundary could be identified clearly were taken 1.5–2 cm proximal to the bifurcation. All images were taken ECG-triggered (frozen on the R-wave). The cursor was manually placed, and measurements of the IMT were made by visual assessment ('leading edge to leading edge'). All measurements were taken by the same experienced operator after standardization according to previously published methods.[19] The coefficient of variation for IMT measurements in our own duplex laboratory was $3 \pm 0.4\%$.

The internal diameter of the CCA which was defined as the distance between the near wall intima-lumen interface to the far wall lumen-intima interface was measured. The mean of six measurements (two in each direction) per side was calculated. Peak systolic velocity (PSV) of the CCA was determined using the smallest possible sample volume—placed in the centre of the vessel keeping the angle between the ultrasound beam and the longitudinal vessel axis between 45 and 59°.

Laboratory tests and calculation of wall shear stress

Blood was drawn from the antecubital vein for determination of hematocrit, white blood cell count, and platelet count using a semi-automated Sysmex K-1000 hematology analyzer (Toa Medical Electronics, Kobe, Japan). Total cholesterol, HDL- and LDL-cholesterol, triglycerides, and fasting glucose were determined by standard established laboratory methods.

Whole blood viscosity was measured in EDTA plasma using a rotational viscometer (Contraves LS 30, Contraves, Switzerland) at high shear rate (94.5/s) at 37 °C.

Peak WSS (dyne/cm^2) was calculated using the formula $4 \times$blood viscosity (Poise)$\times$blood velocity

(cm/s)/internal diameter (cm) as previously described.[20] For calculation, blood velocity values from the right side were taken (values from the left side showed similar results).

Follow-up and endpoint

One day after the procedure and at 1, 3 and 6 months patients were assessed by taking a history to elicit clinical symptoms, by clinical examination (palpation and auscultation of peripheral arteries), pulse volume recordings (oscillography) and determination of ABI at rest.

The day after the procedure and at 6 months, duplex ultrasonography of the treated segment was performed in all patients. Duplex ultrasonography also was performed at any other point of time when the patient reported symptoms of recurrence and/or ABI dropped by >0.1 compared with the immediate postprocedural value. Restenosis was defined by duplex ultrasonography as stenosis $\geq 50\%$ (peak velocity ratio ≥ 2.4) as reported by Ranke *et al.*[21]

Statistical analysis

For data management and most analyses the statistical software package Stat View 5.0. was used. Continuous variables are reported as medians and interquartile ranges, categorical variables as counts and percentages. Two group comparisons at baseline and at 6 months for continuous variables were done by the Mann–Whitney-*U*-test, for categorical variables by Fisher's exact test. Cox proportional hazard analysis was further used to investigate the relation between IMT and WSS and restenosis.

In addition, Kaplan–Meier curves for freedom from restenosis according to the median IMT and to the median WSS were plotted using the S-Plus software. Differences were calculated by the log-rank test.

Results

A total of 31 patients (18 men, 13 women, median age 69 years) were enrolled. One patient was lost to follow-up and one patient died of myocardial infarction. From 29 patients who completed follow-up, 14 (48%) developed restenosis, similar to previous reports.[22,23] Baseline characteristics of the patients according to outcome are shown in Table 1.

Platelet count was lower in patients who restenosed than in those who did not. This confirmed our earlier findings in a different study group.[24] Other parameters did not show any significant differences between patients with or without restenosis (Table 1).

Table 1. Baseline characteristics of patients with and without restenosis at 6 months follow-up

	No restenosis ($N=15$)	Restenosis ($N=14$)	p-Value
Gender (m/f)	9/6	9/5	1.00
Age (years; IQR)	68 (58–78)	69 (58–74)	0.87
BMI	25.9 (23–28)	26.4 (24–29)	0.32
Smoker	13	9	0.18
Pack years	40 (10–60)	22.5 (0–40)	0.27
Diabetes mellitus	6	5	0.43
Arterial hypertension	10	10	1.00
Hypercholesterolemia	9	9	1.00
Severity of PAD			
Stage II	14	13	0.21
Stage III/IV	0	1	
ABI at baseline	0.70 (0.6–0.74)	0.62 (0.53–0.73)	0.29
Stenosis/occlusion	8/7	4/10	0.34
Length of lesion (cm)	4.0 (2–10.5)	7.5 (3–10)	0.65
0–1/2–3 Vessel run-off	5/10	5/9	0.36
PVR at baseline	4 (4–6)	7 (5.2–7)	0.48
History of coronary heart disease	6	4	0.69
History of cerebrovascular disease	3	1	0.59
Total cholesterol (mmol/l)	6.0 (5.5–6.5)	5.5 (5.07–6.35)	0.42
HDL cholesterol (mmol/l)	1.53 (1.32–1.77)	1.43 (1.22–1.47)	0.25
LDL cholesterol (mmol/l)	4.05 (3.9–4.7)	3.70 (3.4–4.5)	0.43
Triglycerides (mmol/l)	1.57 (1.09–1.77)	2.1 (1.14–3.1)	0.12
Blood glucose (mmol/l)	5.8 (5.0–8.7)	5.3 (5.0–6.52)	0.60
Hematocrit (%)	40 (38–42)	38 (34–40)	0.09
Platelets ($\times 10^3/\mu l$)	236 (203–265)	185 (151–245)	0.04
Leukocytes ($\times 10^3/\mu l$)	8.3 (6.7–8.6)	7.35 (6.4–9.0)	0.58

Data are given as medians (interquartilranges) and counts. ABI, ankle-brachial pressure index; PVR, peak velocity ratio.

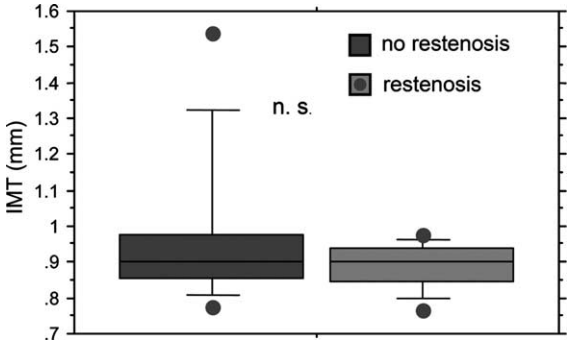

Fig. 1. Baseline carotid intima-media thickness (IMT) in patients with and without restenosis after femoropopliteal PTA, follow-up to 6 months. Boxes show the 10th, 25th, 50th (median), 75th and 90th percentiles; outliers show all observations >90th and <10th percentile; n.s., not significant.

Furthermore, we found no differences in IMT in patients with and without restenosis (Fig. 1).

Kaplan–Meier curves for freedom from restenosis according to the median IMT and to the median WSS are plotted in Fig. 2(A) and (B), respectively.

Morphologic and hemodynamic variables of the common carotid artery are shown in Table 2. No significant differences with regard to carotid WSS, internal diameter, and peak systolic velocity could be found.

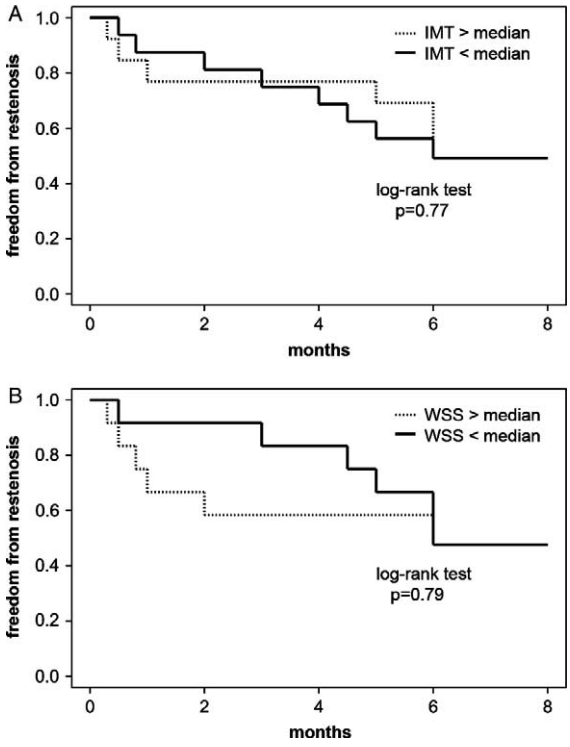

Fig. 2. Kaplan–Meier curves for freedom from restenosis after femoropopliteal angioplasty according to the median IMT (A) and to the median WSS (B).

Blood viscosity was slightly lower in patients without restenosis than in patients with restenosis, but the difference was not significant (Table 2).

The hazard ratio of incident restenosis, as estimated by Cox regression analysis, was 0.04 for IMT ($p=0.23$; 95% CI 0.0001–8.22) and 1.07 for WSS ($p=0.10$; 95% CI 0.98–1.17).

At 6 months follow-up, IMT and WSS were determined in 25 patients. Again we found no differences between patients without and with restenosis (IMT 0.89 (0.77–1.03) *vs.* 0.86 (0.81–0.90), $p=0.71$; WSS 14.6 (9.6–18.7) *vs.* 14.2 (10–18), $p=0.83$).

Discussion

Both the Edinburgh Artery Study[15] and the Rotterdam Study[13] demonstrated a significant association between peripheral vascular disease (PVD) and increased carotid IMT. Although there is emerging evidence that a similar association may exist between femoral IMT and PVD,[25] IMT measured in the carotid artery currently remains the parameter of choice, partly because of the paucicity of data with respect to the predictive value of femoral IMT. Since readily measured, non-invasive parameters, such as IMT, may be used to influence therapeutic decisions, it seemed important to explore the association between carotid IMT and restenosis after femoro-popliteal PTA.

Our data, collected in a relatively small number of patients, suggest for the first time that IMT, measured in the CCA, is not a predictor of restenosis after PTA in the femoro-popliteal segment. Results regarding the role of carotid IMT as a predictor of events after coronary angioplasty are controversial. In one study, an increased carotid IMT was shown to be a predictor of cardiac events such as death, non-fatal acute myocardial infarction or heart failure following PTCA.[26] This study, however, was not designed to explicitly study the association between carotid IMT and restenosis after PTCA. In contrast, a recent previous report[27] failed to demonstrate any association between carotid IMT and restenosis in more than 200 patients undergoing percutaneous coronary intervention. Due to vascular bed heterogeneity, one may not have necessarily expected the same for peripheral arteries. However, our data do not indicate an association between carotid IMT and restenosis after femoro-popliteal PTA. Carotid IMT as measured by ultrasound represents a marker of structural atherosclerosis. The lack of association between carotid IMT and incidence of restenosis may, therefore, reflect the different pathophysiology underlying restenosis, a process which is essentially characterized by

Table 2. Baseline morphologic and hemodynamic parameters of the common carotid artery and blood viscosity in patients with and without restenosis at 6 months follow-up

	No restenosis ($N=15$)	Restenosis ($N=14$)	p-Value
IMT (mm)	0.90 (0.85–0.97)	0.89 (0.84–0.93)	0.51
WSS (dyne/cm^2)	14.1 (11.9–19.2)	15.9 (12.8–21.5)	0.48
V, peak systolic velocity (m/s)	0.63 (0.51–0.79)	0.62 (0.52–0.71)	0.70
Internal diameter (mm)	6.35 (5.51–7.55)	6.94 (6.31–7.95)	0.11
Blood viscosity (mPa.s)	3.8 (3.4–4.0)	4.1 (3.6–4.2)	0.14

Data are given as medians (interquartilranges). IMT, intima-media thickness; WSS, wall shear stress; V, velocity; mPa.s, milli Pascal seconds.

postprocedural endothelial and subendothelial injury, subsequent intimal hyperplasia and proliferation and migration of vascular smooth muscle cells, at least partly mediated by an inflammatory response.

WSS is inversely related to carotid IMT in individuals at low coronary heart disease risk.[28] However, additionally to the lack of association between carotid IMT and restenosis after femoro-popliteal PTA, we also did not observe any relation between carotid WSS and the incidence of restenosis in this particular vascular segment. It is noteworthy that none of the parameters (i.e. blood viscosity, mean or peak systolic velocity, and internal diameter of the CCA) used in the formula to calculate WSS significantly differed between patients who restenosed as compared with those who did not. As shown in an animal model, vascular remodeling after PTA is controlled by both wall stress and shear stress.[29] This clearly implies a role of shear stress in restenosis. However, it has to be pointed out that WSS is considered to be a local rather than a systemic risk factor for arterial remodeling and atherogenesis. As there is always a dynamic interaction between shear stress and systemic risk factors, one may, however, assume an effect on vascular wall behaviour in general.[30] We have recently demonstrated that high WSS, measured by magnetic resonance at the site where angioplasty was performed, is a significant novel predictor for the occurrence of restenosis after PTA in the femoral artery.[31] There are similar findings for WSS measured in the lesion after coronary angioplasty.[32] Based upon these data it is possible that WSS is causally involved in the pathophysiology of restenosis after angioplasty in humans. The fact that we have failed to show an association between WSS within the carotid artery and restenosis in a different artery may suggest that the predictive value of this parameter, at least in the context of restenosis after angioplasty, is only useful when measured locally.

A limitation of the study is the small sample size and the relatively short follow-up period of 6 months. However, IMT and WSS values at 6 months were available in a subgroup of 25 patients. Analyzing these data, we also found no difference at 6 months between patients without and with restenosis. As we did not observe even a modest tendency towards any difference in carotid IMT or WSS between the two groups in this explorative study, we do not consider that a larger study is indicated.

In conclusion, our data may suggest that neither carotid IMT nor carotid WSS are associated with restenosis after femoropopliteal PTA.

Acknowledgements

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